REMARKS

Claims 1-5, 8-11, 14, 24, and 29-34 were pending and examined in the August 6, 2007 Office Action. Claims 1 and 24 have been amended in this reply. No new matter has been added. Accordingly, claims 1-5, 8-11, 14, 24, and 29-34 will be pending upon entry of this amendment.

Claim 1 has been amended to claim with more particularity the type of collagen in the composition for osteoinduction. Support for this amendment is found throughout the specification as filed particularly at page 10, line 26 and page 11, line 20.

Claim 24 has been amended to claim with more particularity the type of collagen used in the claimed method. Support for this amendment is found throughout the specification as filed, particularly at page 10, line 26 and page 11, line 20.

Rejections under 35 U.S.C. § 102(b)

The Examiner has maintained his rejection to claims 1-5 and 8-11 under 35 U.S.C. § 102(b) as anticipated by Boskey *et al.* (1989) *The Journal of Physical Chemistry* 93:1628-1633 (hereinafter "the Boskey article"). The Examiner contends that the Boskey discloses a gel system comprising complexed acidic phospholipids, gelatin and fibrillar collagen. For support, the Examiner cites Boskey, abstract, page 1629, column 2, last paragraph, and Tables II-III. The Examiner believes that the gel system in Boskey would read on the claimed composition comprising acidic-phospholipid complex and collagen. *See* Official Action, pages 4-5.

As shown by the accompanying Declaration of Adele L. Boskey under 37 C.F.R. 1.132 (who is the author of Boskey), the Boskey article does not disclose a gel system that includes complexed acidic phospholipids and fibrillar collagen. The passages cited by the Examiner actually support the opposite and correct conclusion: the gel never includes both components at the same time. The text passages use the conjunction "or" to describe the added components to the gel. Additionally, both Tables II and III list the different results for each of four different macro-molecules added to the gels at separate times. *See* Boskey Declaration, ¶¶ 7 and 8.

The Examiner continues his rejection by stating that "[w]ith respect to 'type I collagen, type II collagen, type IX collagen or mixture thereof' as a suitable gelatin in the instant invention, since there is no indication in the instant claims that said collagen must be essentially in purified or isolated form of 'type I collagen, type II collagen, type IX collagen or a mixture thereof', ... the examiner determines that Boskey's collagen gel system comprising complexed acidic-phospholipids, gelatin and fibrillar collagen anticipates the claimed invention." Official Action, page 5.

It is respectfully submitted that the amendment to claim 1 clarifies that the collagen must be fibrillar. This type of collagen would not include gelatin. As discussed in previous responses, and reiterated in the accompanying Boskey Declaration, gelatin and fibrillar collagen are not the same substance, and one of skill in the art would not think to substitute one for the other. *See* Boskey Declaration, ¶ 9. As set forth above, the Boskey article does not disclose a gel where fibrillar collagen and acidic phospholipids are added simultaneously.

In the Official Action, the Examiner also states that he finds the Applicants' earlier arguments regarding Boskey unpersuasive. In particular, he contends that "[a]pplicant argues that while rat skin collagen fibers are added to the system in Boskey, they are never added in combination with the complexed acidic phospholipids. Furthermore, applicant alleges that Boskey does not disclosed or suggest the currently claimed complex comprising complexed acidic phospholipids and type I, type II or type IX collagen." Official Action, page 2. He then states that he finds this argument unpersuasive because the current invention includes compositions wherein the acidic phospholipids and collagen are complexed, and those which they are not. *See* Official Action, pages 2-3.

The Applicants do argue in the previous response and above, that the Boskey article, when correctly interpreted, does not teach or disclose the presently claimed invention. However, whether the acidic phospholipids and collagen are complexed or not has no bearing on the issues of anticipation or obviousness. The gels in Boskey never contain both components at the same time. Boskey does not disclose a gel where the acidic phospholipids and collagen are simultaneously present, thus, the two can never be in combination, either in complex or not. *See* Boskey Declaration, ¶ 8. Additionally, there is no suggestion in the Boskey article to combine

acidic phospholipids and collagen in a single gel, as the reference discloses that collagen does not promote mineral growth. *See* Boskey Declaration, ¶ 10.

For all of these reasons, claims 1-5 and 8-11 are not anticipated by Boskey.

Rejections under 35 U.S.C. § 103

The Examiner rejects claims 24 and 29-34 under 35 U.S.C. § 103 as obvious over U.S Patent No. 6,311,690 issued to Jefferies ("Jefferies") in view of U.S. Patent No. 4,578,384 issued to Hollinger ("Hollinger"). Specifically, the Examiner contends that Jefferies teaches a collagen-calcium conjugate or a reconstituted collagen and acidic phospholipid conjugate that is useful in inducing bone growth. The Examiner further states that Jefferies differs from the present invention in the use of polyglycolic acid and the specific dosage amounts. Hollinger is being used as a supplemental reference to demonstrate the use of bicompatible copolymer such as polyglycolic acid and polyactic acid. The dosages, the Examiner contends, are within the skill of the art. *See* Official Action, pages 6-8.

This rejection is respectfully traversed.

In order to make a showing of obviousness, the Examiner must make the four factual inquiries set forth in *Graham v. John Deere*, 383 U.S. 1, 17-18 (U.S. 1966): (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the pertinent art; and (4) evaluating evidence of secondary considerations. *See KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727, 1734, 167 L.Ed.2d 705, 715 (2007). The Examiner can also rely upon the teaching, suggestion or motivation test to provide insight as to whether the claimed invention is obvious. *KSR*, 127 S.Ct. at 1731. The Examiner has not done that here.

Jefferies discloses a product and process comprising collagen and demineralized bone particles (Jefferies, abstract). The collagen that forms the organic matrix is reconstituted collagen (Jefferies, column 4, lines 58-59) which is said to provide a matrix with unique and unexpected strength (Jefferies, column 5, lines 61-63). Demineralized bone particles are bound to this organic matrix (Jefferies, column 4, lines 11-16). Jefferies notes that acidic phospholipids

can strengthen the matrix (Jefferies, column 6, lines 35-36; Example 12). However, the specific components of the acidic phospholipids are not disclosed in Jefferies.

Hollinger discloses a material consisting of a combination of a phospholipid and a biodegradeable, biocompatible copolymer that is an alternative for the agents that were commonly being used at the time, such as bone grafts and implants, collagen gels, ceramics, bone derivatives, and biopolymers. *See* Hollinger, abstract; column 2, lines 37-51.

The presently claimed method comprises applying an effective growth stimulating amount of a complexed-acidic-phospholipid-collagen composite where the composite comprises calcium, phospholipid, inorganic phosphate, and fibrillar collagen. The differences between the teachings in the prior art reference and the presently claims are too great for such claims to be obvious over the references.

To start, Jefferies does not teach the all of the specific components of the complexed acidic phospholipid called for in the present claims, specifically inorganic phosphate and calcium. As set forth in the present disclosure, acidic phospholipids form unique complexes when incubated with inorganic phosphate and calcium These complexes exist in mineralizing tissue as part of the nucleational core of the extracellular matrix, the site of initial mineral deposition in cartilage, mantle dentin, and newly forming bone. Additionally, these complexes induce hydroxyapatite formation *in vitro* and when implanted, *in vivo*. *See* specification, page 3, lines 10-24. There is no teaching or suggestion of the complexed acidic phospholipids comprising phospholipid, inorganic phosphate and calcium called for in the present claims nor of their ability to induce hydroxyapatite formation in Jefferies, and the missing limitations are not supplied by Hollinger.

Additionally, the present claims have been amended to cover a complex comprising fibrillar collagen. Jefferies does not teach or suggest the use of fibrillar collagen, and specifically states that reconstituted collagen, and as well as the reconstitution method, has a direct effect on the strength of the matrix (Jefferies, column 5, lines 59-65). A matrix with unique strength properties is the objective of the Jefferies invention. *See* Jefferies, column 4,

lines 33-36. Thus, Jefferies does not teach or suggest the use of fibrillar collagen in a method for bone growth. Hollinger specifically states that his material is to be used in place of collagen.

The Examiner should also consider the evidence of unexpected results set forth in the application. These include lack of rejection of implant material, consistent bone growth across the region in need of growth without the disadvantages of rapid degradation of the composite material, cost-effectiveness, greater osteoinduction than collagen alone and/or in combination of non-stable peptides, and the lack of denaturation during standard sterilization procedures. *See* specification, page 6, lines 27 - page 7, line 2 and page 14, line 28 - page 5, line 10. It should be noted that the first listed advantage, the lack of rejection, is especially surprising and unpredictable in view of the teachings of Hollinger regarding the unwanted immune response of natural materials, such as collagen.

The Examiner also states that he finds the Applicants' arguments that there is no suggestion to combine the references unpersuasive and states that one would have been motivated to combine Jefferies and Hollinger because they are drawn to the same technical fields and constitute the same ingredients. Official Action, page 3. It is respectfully submitted that this assertion is incorrect.

Jefferies and Hollinger do not teach methods that use the same ingredients. Hollinger teaches a material consisting of a combination of proteolipid and biodegradeable, biocompatible copolymer for the healing of osseous tissue. Hollinger further discloses that this "represents a significant improvement over conventional materials" such as collagen and bone derivatives. *See* Hollinger, column 2, lines 38-50. Jefferies on the other hand, discloses the use of the "conventional materials" of reconstituted collagen and bone.

In view of this teaching in Hollinger, there would have been no reason to combine the teachings of these two references as this patent teaches away from Jefferies because Jefferies uses the materials, *e.g.*, collagen and bone particles, that promote unwanted immune responses, and over which Hollinger "represents a significant improvement." *See In re Lundsford,* 148 U.S.P.Q. 721, 726 (CCPA 1966). Given that Hollinger states that the materials used in Jefferies would be undesirable and likely cause an unwanted immune reaction, and that Hollinger suggests

that the result of combining the two would not achieve a desirable result, a person of ordinary skill in the art would have had no motivation or reason to combine the teachings of the two references. *See Tec Air Inc. v. Denos Mfg. Mich., Inc.,* 192 F.3d 1353, 1360 (Fed. Cir. 1998).

The Examiner's own citation in support of his assertion actually teaches away from combining the material disclosed in Hollinger with the material disclosed in Jefferies. *See* Official Action, page 7; *see also* Official Action dated March 8, 2007, page 7-8; *see also* Hollinger, column 14, lines 28-32 ("The results of applicant's evaluation indicate that copolymer-proteolipid implant material was very successful at stimulating the early phases of bone repair and that it can be used *as an unexpectedly superior alternative to the agents commonly employed for bone repair and reconstruction.*" (emphasis added)). The Examiner has not explicitly shown that there would have been a suggestion and/or a motivation to combine the teachings of these two references.

For all of these reasons, claims 24 and 29-34 are not obvious in view of Jefferies combined with Hollinger and the rejection on this ground should be withdrawn.

It is duly noted that claim 14 appears to be free of any prior art rejections.

CONCLUSION

In view of the above amendments and remarks, it is respectfully submitted that the pending claims are now in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution of this case, the Examiner is respectfully requested to call the undersigned attorney at (212) 527-7631. The Examiner is hereby authorized to charge any additional fees associated with this response to our Deposit Account No. 04-0100.

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Respectfully submitted,

By _____

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